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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/282,879	03/31/1999	SUBROTO CHATTERJEE	46906-2-DIV	9227
21874	7590	10/25/2004	EXAMINER	
EDWARDS & ANGELL, LLP P.O. BOX 55874 BOSTON, MA 02205			RAO, MANJUNATH N	
		ART UNIT	PAPER NUMBER	
		1652		

DATE MAILED: 10/25/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

<b>Office Action Summary</b>	Application No.	Applicant(s)
	09/282,879	CHATTERJEE, SUBROTO
	Examiner Manjunath N. Rao, Ph.D.	Art Unit 1652

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

#### Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

#### Status

1) Responsive to communication(s) filed on 10 August 2004.  
 2a) This action is FINAL.      2b) This action is non-final.  
 3) Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

#### Disposition of Claims

4) Claim(s) 13-17 and 32-37 is/are pending in the application.  
 4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.  
 5) Claim(s) \_\_\_\_\_ is/are allowed.  
 6) Claim(s) 13-17 and 32-37 is/are rejected.  
 7) Claim(s) \_\_\_\_\_ is/are objected to.  
 8) Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

#### Application Papers

9) The specification is objected to by the Examiner.  
 10) The drawing(s) filed on \_\_\_\_\_ is/are: a) accepted or b) objected to by the Examiner.  
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).  
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).  
 11) The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

#### Priority under 35 U.S.C. § 119

12) Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
 a) All    b) Some \* c) None of:  
 1. Certified copies of the priority documents have been received.  
 2. Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
 3. Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

#### Attachment(s)

1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892)	4) <input type="checkbox"/> Interview Summary (PTO-413)
2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948)	Paper No(s)/Mail Date. _____
3) <input type="checkbox"/> Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____	5) <input type="checkbox"/> Notice of Informal Patent Application (PTO-152)
	6) <input type="checkbox"/> Other: _____

## **DETAILED ACTION**

Claims 13-17 and 32-37 are currently pending and are present for examination.

Applicants' amendments and arguments filed on 8-10-2004, have been fully considered and are deemed to be persuasive to overcome the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. Specifically, Examiner has withdrawn the previous two rejections under 35 U.S.C. 112, 2<sup>nd</sup> paragraph in view of claim amendments.

### ***Claim Objections***

Claim 15 is objected to because of the following informalities: a) In line 2, the first step under step "I" is indicated by a capital "I" as opposed to "i"; b) in line 5 the word "presence" is spelt as "present". Appropriate correction is required.

Claim 34 is objected to because of the following informalities: Claim 34 ends with two periods. Appropriate correction is required.

Claim 35 objected to because of the following informalities: in line 5 the word "presence" is spelt as "present". Appropriate correction is required.

### ***Claim Rejections - 35 USC § 112***

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 13, 34 and claims 14, 16-17, 32-33 which depend from claim 13 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. Claims 13 and

34 are drawn to a method of identifying a compound useful in the treatment of a human neutral sphingomyelinase related disorder, comprising contacting a candidate pharmacological agent with a recombinant human neutral sphingomyelinase having an amino acid sequence represented by SEQ ID NO:2 or a fragment or a derivative of SEQ ID NO:2, followed by analyzing the mixture of the candidate agent and the enzyme or the fragment or derivative thereof, wherein the analyzing step further comprises comparing enzyme activity in the presence and absence of the agent. However, it is not clear to the Examiner as to which candidate agent is further selected as useful, i.e., the candidate compound which reduced the enzyme activity (an inhibitor/antagonist) or the candidate compound which in fact increased the enzyme activity (agonist).

In response to the previous Office action, while applicants have addressed the other issues that were part of the previous rejection, they seem to have ignored that above aspect of the rejection. Hence the above rejection is maintained.

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 13, 15-17, and 32-33 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of identifying a compound useful in the diagnosis or treatment of a human neutral sphingomyelinase related disorder comprising contacting a pharmacological agent with a recombinant human neutral sphingomyelinase having an amino acid sequence represented by SEQ ID NO:2 or a fragment thereof having the neutral sphingomyelinase activity, does not reasonably provide enablement for such a method wherein a

derivative (which Examiner has broadly interpreted to include mutants and variants) of the same (i.e., SEQ ID NO:2), having at least about 50% of the neutral sphingomyelinase activity of SEQ ID NO:2 or wherein said derivative has an amino acid sequence that is at least 70% identical to SEQ ID NO:2 is used. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make the invention commensurate in scope with these claims.

Factors to be considered in determining whether undue experimentation is required, are summarized in *In re Wands* (858 F.2d 731, 8 USPQ 2nd 1400 (Fed. Cir. 1988)) as follows: (1) the quantity of experimentation necessary, (2) the amount of direction or guidance presented, (3) the presence or absence of working examples, (4) the nature of the invention, (5) the state of the prior art, (6) the relative skill of those in the art, (7) the predictability or unpredictability of the art, and (8) the breadth of the claim(s).

Claims 13, 15-17, and 32-33 are so broad as to encompass a method of use of any variants or mutants of SEQ ID NO:2 or any sphingomyelinase having an amino acid sequence that is at least 70% identical to SEQ ID NO:2 for identifying a compound useful in diagnosis or treatment of human sphingomyelinase disorder. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of sphingomyelinases broadly encompassed by the claims. Since the amino acid sequence of a protein determines its structural and functional properties, predictability of which changes can be tolerated in a protein's amino acid sequence to obtain the desired activity requires a knowledge of and guidance with regard to which specific amino acids in the protein's sequence, if any, are tolerant of modification and which are conserved (i.e. expectedly intolerant to modification), and

detailed knowledge of the ways in which the proteins' structure relates to its function. However, in this case the disclosure is limited to the nucleotide and encoded amino acid sequence of only a single sphingomyelinase. It would require undue experimentation of the skilled artisan to make and use the claimed polypeptides with said function/activity. The specification is limited to teaching the use of SEQ ID NO: 2 as a sphingomyelinase but provides no guidance with regard to the making of variants, mutants, derivatives or with regard to other uses. In view of the great breadth of the claim, amount of experimentation required to make the claimed polypeptides for use in the above claimed method, the lack of guidance, working examples, and unpredictability of the art in predicting function from a polypeptide primary structure (e.g., see Ngo et al. in *The Protein Folding Problem and Tertiary Structure Prediction*, 1994, Merz et al. (ed.), Birkhauser, Boston, MA, pp. 433 and 492-495, Ref: U, Form-892), the claimed invention would require undue experimentation. As such, the specification fails to teach one of ordinary skill how to make and use the full scope of the polypeptides for the method encompassed by this claim.

While recombinant and mutagenesis techniques are known, and it is routine in the art to screen for multiple substitutions or multiple modifications, as encompassed by the instant claims, the positions (i.e., amino acid residues) within a protein's sequence where amino acid modifications can be made with a reasonable expectation of success in obtaining the desired activity/utility are limited in any protein and the result of such modifications is unpredictable. In addition, one skilled in the art would expect any tolerance to modification for a given protein to diminish with each further and additional modification, e.g. multiple substitutions.

The specification does not support the broad scope of the claims which encompasses the making and using of all polypeptide derived from SEQ ID NO:2 (i.e., derivatives) or the

making and using of all polypeptides having 70% amino acid sequence identity with SEQ ID NO:2 (i.e., amino acid sequence with 70% identity to the enzyme of SEQ ID NO:2) because the specification does not establish: (A) regions of the protein structure which may be modified without affecting sphingomyelinase activity; (B) the general tolerance of sphingomyelinases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue in SEQ ID NO:2 with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Thus, applicants have not provided sufficient guidance to enable one of ordinary skill in the art to make and use the claimed invention in a manner reasonably correlated with the scope of the claims broadly including sphingomyelinases with an enormous number of amino acid modifications. The scope of the claims must bear a reasonable correlation with the scope of enablement (*In re Fisher*, 166 USPQ 19 24 (CCPA 1970)). Without sufficient guidance, determination of sphingomyelinases required for the above method having the desired biological characteristics is unpredictable and the experimentation left to those skilled in the art is unnecessarily, and improperly, extensive and undue. See *In re Wands* 858 F.2d 731, 8 USPQ2nd 1400 (Fed. Cir, 1988).

In response to the previous Office action applicant has traversed the above rejection arguing at length. First of all Examiner would like to draw the attention of the applicant to the above modified rejection in which, Examiner argues that the specification is not enabled for the method requiring the use of derivatives of SEQ ID NO:2 and/or mutants and variants of SEQ ID

NO:2 (i.e., sequences that are 70% identical to SEQ ID NO:2). Fragments of SEQ ID NO:2 having the sphingomyelinase activity have been considered as enabled.

Applicant argues that specific examples of acceptable N-Smases are disclosed throughout the present application and provides examples such as page 7, lines 19-26, page 8, lines 16-23 as well as Example 6 (see page 6 and 7 of Remarks filed on 8-10-04). However, a perusal of the specification at the above pages provide generalized information of only SEQ ID NO:2. Furthermore, it must be noted that the specification has a record of only two examples and Examiner was unable to locate "Example 6". In summary, applicant vehemently disagrees with the above rejection and reiterates that the specification provides the chemical structure of the native N-Smase both at the amino acid and nucleic acid levels and important function domains in the structure have been recognized and methods for producing suitable N-Smases, preferably by use of conventional recombinant means have been disclosed and therefore, any testing needed to identify or confirm suitable N-Smases for use with the claimed invention is well within the level of experimentation permitted by the Federal Circuit. *In re Wands*, 8 USPQZd 1400 (Fed. Cir. 1988). Examiner respectfully disagrees with such an argument to be persuasive to overcome the above rejection. This is because contrary to applicant's argument while the specification does provide the structure and function of SEQ ID NO:2, and discusses as to what types of variants of SEQ ID NO:2 can be used in the method, it does not provide any guidance as to how to make such variants or derivatives.

Applicant continues the argument that a worker in this field would be able to use the guidance provided by the instant disclosure to select appropriate N-Smases and any inoperable embodiments of the type described by the rejection could be readily avoided. While that may be

so, the specification first of all lacks any guidance to make the variants, mutants and derivatives and therefore, any guidance to select appropriate N-Smases is moot.

Next applicant submits that one of skill having read applicant's disclosure would know to identify suitable N-Smases in addition to the native enzyme and that even if one assumes for the sake of argument that a particular N-Smase fragment or derivative did not exhibit acceptable activity, that result, by itself, would not support the present enablement rejection and the worker would understand that another fragment or derivative as provided by the specification, could be tested and identified for suitable activity and that the rejection has not provided any reason to doubt that the guidance provided by applicant's disclosure could not be used to identify a range of acceptable N-Smases for use with the claimed methods. Examiner respectfully disagrees with such a line of argument. This is because, without any guidance to make the variant or mutant or derivative, the question of testing them and identifying only those that have suitable activity does not arise at all. Hence all such arguments are tangential to the crux of the problem and that is the lack of specific guidance in the specification to make the variants, mutants and derivatives of SEQ ID NO:2. Examiner reiterates that while methods to produce variants of a known amino acid sequence, such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan, producing variants as claimed by applicants requires that one of ordinary skill in the art know or be provided with guidance for making specific amino acid changes in SEQ ID NO:2, i.e., a rational and predictable scheme for modifying any amino acid residue with an expectation of obtaining the desired biological function followed by the selection of which of the large number of variants have the claimed property (i.e., sphingomyelinase activity). Without such guidance one of ordinary skill would be reduced to the necessity of producing and testing

all of the virtually infinite possibilities. This would clearly constitute undue experimentation. While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed (i.e., which specific amino acid residues can be modified by either substitution (with any other specific amino acid), deletion, addition etc.). Such guidance has not been provided in the instant specification. As previously stated the specification does not establish: (A) regions of the protein structure which may be modified without affecting sphingomyelinase activity; (B) the general tolerance of sphingomyelinases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue in SEQ ID NO:2 with an expectation of obtaining the desired biological function; and (D) the specification provides insufficient guidance as to which of the essentially infinite possible choices is likely to be successful.

Finally, applicant argues that the Office has acknowledged on record the high level of knowledge in the art of enzymology and such knowledge is presumed to include information about N-Smases as acceptable fragments and derivatives of that enzyme. Examiner respectfully disagrees with such an argument. Yes, the Office acknowledged the high level of knowledge in the art of enzymology in general but to argue that such acknowledgement included the knowledge of making specific variants of N-Smases having an amino acid sequence of SEQ ID NO:2 is highly misplaced. For all the above reasons Examiner continues to maintain the above rejection.

Claims 13 and 15-17, 32-33 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claims 13 and 15-17, 32-33, are directed to a method of use of polypeptide derivatives corresponding to the sequence of SEQ ID NO:2. Claims 13 and 15-17, 32-33 are rejected under this section of 35 USC 112 because the claims are directed to a method of use of a genus of polypeptides derived from SEQ ID NO:2 including modified polypeptide sequences, (modified by at least one of deletion, addition, insertion and substitution of an amino acid residue in SEQ ID NO:2) that have not been disclosed in the specification. No description has been provided of the modified polypeptide sequences encompassed by the claim. No information, beyond the characterization of SEQ ID NO:2 has been provided by applicants which would indicate that they had possession of the genus of derived polypeptides for use in the claimed method. The specification does not contain any disclosure of the structure of all the polypeptide sequences derived from SEQ ID NO:2, within the scope of the genus for use in the claimed method. The genus of polypeptides for use in the claimed method is a large variable genus including peptides which can have a wide variety of structures. Therefore many structurally unrelated polypeptides are encompassed within the scope of these claims. The specification discloses only a single species (i.e., SEQ ID NO:2) of the claimed genus which is insufficient to put one of skill in the art in possession of the attributes and features of all species within the claimed genus. Therefore, one skilled in the art cannot reasonably conclude that applicant had possession of the claimed invention at the time the instant application was filed.

Applicant is referred to the revised guidelines concerning compliance with the written description requirement of U.S.C. 112, first paragraph, published in the Official Gazette and also available at [www.uspto.gov](http://www.uspto.gov).

In response to the above rejection, applicants addressed it as an enablement rejection (see page 9 of remarks filed on 8-10-04) and submit that claim 13 has been amended with language from claim 31. Respectfully, such an amendment has not overcome the issue of written description. Hence the above rejection is maintained.

***Claim Rejections - 35 USC § 103***

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

Claims 13-17 and 32-37 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chatterjee et al. (J. Biol. Chem., 1989, Vol. 264(21):12554-12561), Ogita et al. (WO 9518119, 7-6-1995) and Ausubel et al. (Current Protocols in Molecular Biology, John Wiley and Sons, 1987, pages 10.0.3-10.0.6). Claims 13-17 and 31 in this instant application are drawn to a method of identifying a compound which when used in a reaction comprising sphingomyelin as the substrate, the neutral sphingomyelinase as the enzyme and ceramide as the cleaved product, leads to reduced concentration of the cleavage product such that the identified compound could be used in the diagnosis or treatment of human neutral sphingomyelinase related disorder.

Chatterjee et al. teach an assay method for the activity of neutral sphingomyelinase wherein a mixture of sphingomyelin is treated with the enzyme sphingomyelinase under conditions wherein the substrate is cleaved and cleaved product, ceramide is detected (see page 12555, 2nd column). Chatterjee et al. also teach that sphingomyelinase catalyzes the hydrolysis of sphingomyelin to ceramide and phosphorylcholine at both acidic and neutral pH. The reference also teaches that the study of neutral sphingomyelinases are necessary in view of its involvement in gentamicin-mediated nephrotoxicity in man and also due to the involvement of sphingosine, released as a consequence of the action of sphingomyelinase, in a cascade of reactions leading to the regulation of protein kinase C activity (see page 12554, Introduction). Thus it appears that the substrate, cleavage product and the importance of the sphingomyelinase reaction was common knowledge in the art. However, while the above reference teaches a purified SM and an assay for its activity, it does not teach a recombinant SM or the use of recombinant SM in an assay for detection of a pharmacological agent even though the activity assay for the purified enzyme could be used for the same.

Ogita et al. teach the manufacture of a sphingomyelinase inhibitor obtained from a microorganism and its use to treat a variety of diseases and disorders such as HIV, diabetes, leukemia, cachexia etc. Ogita et al. also teach an assay for determining the inhibitory activity of a compound using sphingomyelinase isolated from a rat brain wherein the assay is performed at a pH of 7.5 very close to the neutral pH. However, this reference also does not teach the use of recombinant SM.

Ausubel et al. in their voluminous manual teach all the techniques related to cloning a known protein starting from its purification stage up to obtaining its cDNA and the recombinant

form of the protein. Examiner draws the attention of the applicant to the enclosed pages 10.0.3-10.0.6 wherein the reference teaches how one can obtain the oligonucleotide probe from a purified protein. Other chapters in the book also teach how one skilled in the art can make a specific cDNA library and use the oligonucleotide probe to clone the specific protein and obtain it in the recombinant form.

With the purified SM as taught by Chatterjee et al. and the knowledge existing in the art of protein biochemistry and molecular biology to make recombinant proteins and the importance of sphingomyelinase inhibitors as taught by Ogita et al., it would have been obvious to one skilled in the art at the time the invention was made to use the purified protein of Chatterjee et al., obtain a cDNA clone and make recombinant sphingomyelinase using the techniques of Ausubel et al. and use it to develop a method of identifying other compounds which inhibit sphingomyelinase on line with Ogita et al. such that compounds could become useful in diagnosis or treatment of a human neutral sphingomyelinase related disorder. Chatterjee et al. teach that one of ordinary skill in the art would be motivated to do this in order to study the biochemical mechanisms involved in gentamicin-mediated nephrotoxicity or in Niemann-Pick disease and Ogita et al. teach that one of ordinary skill in the art would be motivated to do this because, when the transmission of signals introduced by IL-1 $\beta$  and TNF- $\alpha$  are blocked by inhibiting the activity of sphingomyelinase using an inhibitor, the symptoms of various diseases related to cytokines can be improved. One would have a reasonable expectation of success since Chatterjee et al. provide a purified sphingomyelinase and a robust and time tested assay method and Ogita et al. provide an assay and demonstrate the existence of a chemical compound which

inhibits sphingomyelinase and Ausubel et al. provide time tested recombinant techniques that has been used by a number of other inventors.

Therefore the claimed invention would have been *prima facie* obvious to one of ordinary skill in the art.

Arguing against the above rejection applicant maintains that the USPTO position is completely at odds with the record of the case and provides no objective evidence that one could obtain amino acid sequences of the pending claims in view of the cited art and that one of skill could certainly not obtain the nucleic acid encoding the featured protein absent the painstaking work performed by the inventor and his collaborators. Examiner respectfully disagrees with such a line of argument. While Examiner has provided the motivation and reasons for reasonable expectation of success applicants have provided no reasonable arguments as to why their invention would not have been obvious to those skilled in the art except for the argument that "absent the painstaking work" by the inventor those skilled in the art would not have arrived at the recombinant enzyme in order to perform the above method.

Applicant alleges that the Office simply continues to disregard actual scientific evidence on grounds that applicant should have been able to overcome his problems. Examiner would like to remind the applicants that they are claiming a method of use of a polypeptide that is already purified in the prior art but not actually claiming the recombinant N-Smases polypeptide, under which condition, applicant's argument of the difficulty of getting the cDNA clone may have added weight against an obviousness rejection. As stated earlier, the procedures to obtain the cDNA clone may have been painstaking but the use of recombinant form of a protein that is already well known in the art is obvious as stated above. Therefore, contrary to all the

arguments by the applicant against the rejection, Examiner continues to maintain his position that claims 13-17, 32-37 are *prima facie* obvious over Chatterjee et al., Ogita et al. and Ausubel et al.

***Conclusion***

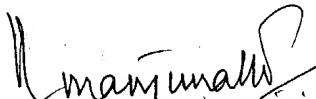
None of the claims are allowable.

**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the Examiner should be directed to Manjunath N. Rao, Ph.D. whose telephone number is 571-272-0939. The Examiner can normally be reached on 7.00 a.m. to 3.30 p.m. If attempts to reach the examiner by telephone are unsuccessful, the Examiner's supervisor, Ponnathapura Achutamurthy can be reached on 571-272-0928. The fax phone numbers for the organization where this application or proceeding is assigned is 703-872-9306/9307 for regular

communications and for After Final communications. Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is 571-272-1600.



Manjunath N. Rao, Ph.D.  
Primary Examiner  
Art Unit 1652

October 21, 2004